REMARKS

In the amendments presented herein, claims 4, 7 and 8 have been amended. Support for the amendments can be found throughout the specification (including the claims) as originally filed. No new matter has been added.

Now pending in the application are claims 1-10; claims 1-3, 5, 6, 9 and 10 stand withdrawn from consideration, so claims 4, 7 and 8 are under examination.

The amendment and/or cancellation of claims is without prejudice or disclaimer of the subject matter thereof and was done solely to expedite prosecution of the present application. Applicants reserve the right to pursue the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter.

Objections to the Claims

The Examiner objected to claim 4 as allegedly being of improper dependent form. Without agreeing with the Examiner's objection, and solely to expedite prosecution, claim 4 has been amended and is now an independent claim. Applicants submit that the objection has been overcome.

The Examiner objected to claim 8 for reciting the language "highly possible or has high possibility." Without agreeing with the Examiner's objection, and solely to expedite prosecution, claim 8 has been amended and no longer recites this language. Applicants submit that the objection has been overcome.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claims 4, 7 and 8 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is traversed.

The Examiner states that claim 4 encompasses "a method of evaluating the possibility of onset or onset of rheumatoid arthritis . . . in 'any' subject or 'any mutation'." Office Action at page 4. This statement is traversed. Claim 4, as amended is directed to a method of evaluating onset or onset possibility of rheumatoid arthritis in a human subject, and the method comprises detecting the presence or absence of a gene coding

a protein comprising the amino acid sequence shown in SEQ. ID NO.:1. Thus, the claim does not encompass methods in "any" subject nor detection of "any" mutation.

The Examiner further states that "it is unclear from the specification whether the deletion taught in figure 4 of the specification encompasses SEQ ID NO.1 with glycine at positions 269 and 270, or a glycine at position 269, or no glycine at positions 269 and 270." Office Action at page 4. Applicants disagree and offer the following remarks.

The protein of SEQ ID No.:1 is the mutant protein, in which a Gly is inserted at position 269. See, e.g., the specification at the paragraph bridging pages 7-8, and at pages 24-26, and Figure 3. The wild-type protein does not have a Gly at position 269. Similarly, the gene of SEQ ID No.:2 is the mutant gene, in which a GGT is inserted at bases 805-807; this gene encodes the mutant protein of SEQ ID NO.:1.

In Figure 4, the indicator "nt805(del3) homo" refers to the number of people having the normal gene homozygously, and the indicator "nt805(del3) hetero" refers to the number of people having the mutant gene heterozygously. In Figure 4, the indicator "nt805 homo" refers to the number of people having the mutant gene homozygously.

As shown in Figure 4, both in RA families and Sporadic families, only the RA patients have "ny805 homo" (homozygous 3-base-insertion mutation). Further, in the "nt805(del3 homo" and "nt805(del3) hetero" groups, there is a significant difference between RA patients from the Sporadic families and healthy subjects from Sporadic families, and between RA patients from the Sporadic families and healthy subjects from RA families. This finding shows the tendency for RA patients to have the mutant protein and the mutant gene, while healthy subjects have neither the mutant protein nor the mutant gene. Thus, the mutant protein and gene are associated with RA onset or onset possibility.

Therefore, detection of the 3-base insertion mutation in the gene makes possible evaluation of the onset, or possibility of RA onset, in a subject.

Claim 4, as amended , is directed to method of evaluating onset or onset possibility of rheumatoid arthritis in a human subject, the method comprising the step of: detecting the presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject.

From the foregoing, it will be appreciated that the method of claim 4 includes detecting the presence or absence of the mutant gene (the gene associated with RA onset).

In his Wands analysis, the Examiner stated (referring to Figure 5) that the "specification does not teach if the RA patients are homozygous or heterozygous for the 'GGT' insert or deletion", and that "the ability to correlate this decreased mRNA with RA is however unclear." Office Action at page 6. Applicants disagree and offer the following remarks.

In Figure 5, an amount of expressed "whole Angiopoietin-1 mRNA" was measured. More specifically, wild-type Angiopoietin-1 mRNA and the mutant Angiopoietin-1 mRNA were not differentiated in Figure 5; that is, an amount of an expressed mRNA derived from whole Angiopoietin-1 gene, which includes both wild-type Angiopoietin-1 gene and mutant Angiopoietin-1 gene, were measured in Figure 5.

As shown in Figure 5, RA patients have a significantly smaller amount of expressed Angiopoietin-1 mRNA (whole Angiopoietin-1 mRNA) compared to healthy subjects. Furthermore, the finding that "the mutant Angiopoietin-1 gene is associated with the onset of RA," as shown in Figure 4, and the finding that "a whole amount of expressed Angiopoietin-1 mRNA is related to the onset of RA," as shown in Figure 5, are common only in relation to the onset of RA. The threshold values 1 and 2 are defined specifically in the specification and examples for determining the threshold values are also provided (see, e.g., pages 29-30).

Still further, in his Wands analysis, the Examiner states that certain references teach that "correlating gene expression level to any phenotypic quality" is unpredictable (Office Action at page 7). However, Applicants note that the cited references relate to detection of expression of multiple genes, e.g., using microarrays. While it may in some cases be difficult to evaluate onset of certain diseases or conditions by correlating gene expression levels using such microarrays, the present invention (in certain embodiments) is directed to measurement of the expression level of a single gene (Angiopoietin-1). As shown in Example 4 of the present specification, quantitative PCR can be used for this purpose. Therefore, Applicants submit that evaluating onset or onset possibility of disease according to the present invention can be readily performed by one of ordinary skill in the art.

The Examiner also states that "one would first have to determine if the claimed invention encompasses SEQ ID NO.1 with a glycine at positions 269 and 270, or a glycine at position 269, or no glycine at position 269 or 270." Office Action at page 8. Applicants disagree. The specification clearly describes the wild-type and mutant Angiopoietin-1 proteins and genes encoding them; no experimentation would be required to determine the sequence of the mutant protein and gene. Moreover, claim 4 (as amended) recites that the method comprises detecting the presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1. One of skill in the art would be able to perform the claimed methods without undue experimentation. In addition, the Examiner's reference to "dogs, cats, mice" and the like are irrelevant to the pending claims, which are directed human subjects.

Applicants respectfully contend that the specification provides enablement for the full scope of the pending claims, and, furthermore, that the claims meet all the requirements of, *inter alia*, 35 USC §112. Reconsideration and withdrawal of the rejection is requested.

Rejection under 35 U.S.C. §112, first paragraph (written description)

Claim 4 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. This rejection is traversed.

The Examiner states that claim 4 encompasses "any" mutation (Office Action at page 10). However, as discussed above, claim 4 does not encompass "any mutation, but rather is directed to a method comprising detection of the presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1. Claim 4 clearly complies with the written description requirement.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

Rejection under 35 U.S.C. §112, second paragraph

Claims 4, 7 and 8 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is traversed.

Without agreeing with the Examiner's position, and solely to expedite prosecution of the application, claim 4 has been amended, and now recites a method comprising the step of detecting the presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject. Applicants submit that claim 4 does not lack a positive active step relating back to the preamble, and is not indefinite. Further, as described above, claim 4 is directed to a method of evaluating onset or onset possibility of rheumatoid arthritis in a human subject (not "any" subject as stated by the Examiner), by detecting the presence or absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 (not detecting "any" mutation as stated by the Examiner).

Without agreeing with the Examiner's position, and solely to expedite prosecution of the application, claim 7 has been amended, and now recites a method comprising the step of measuring an amount of an expressed RNA derived from whole Angiopoietin-1 gene, and evaluating the onset or onset possibility of rheumatoid arthritis in the subject. Applicants submit that claim 7 does not lack a positive active step relating back to the preamble, and is not indefinite.

Claim 8 was rejected as indefinite because "threshold values 1 and 2 are not defined." This rejection does not apply to pending claim 8, which provides that threshold value 1 corresponds to the average amount of expressed angiopoietin-1 mRNA in RA subjects, and threshold value 2 corresponds to the average amount of expressed angiopoietin-1 mRNA in normal subjects.

Applicants therefore contend that the rejection has been overcome and should be withdrawn, and such action is requested.

Rejection under 35 U.S.C. §102(b)

Claims 4 and 7 stand rejected under 35 U.S.C. §102(b), as allegedly anticipated by Davis et al. This rejection is traversed.

Applicants submit that the Davis et al. reference discloses the wild-type angiopoietin sequence but not the mutant (Gly269 insertion) sequence of SEQ ID No.:1. The Davis reference cannot anticipate claim 4 as amended, in which the presence or

absence of a gene coding a protein comprising the amino acid sequence shown in SEQ. ID NO.:1 (the mutant protein) is detected in a subject. The Davis reference also does not disclose a method according to amended claim 7, in which an amount of an expressed mRNA derived from whole Angiopoietin-1 gene, including wild-type Angiopoietin-1 gene and mutant Angiopoietin-1 gene, is measured, and the onset or onset possibility of rheumatoid arthritis in the subject is evaluated. The Davis reference does not teach or suggest that an amount of an expressed mRNA derived from whole Angiopoietin-1 gene, including wild-type Angiopoietin-1 gene and mutant Angiopoietin-1 gene, can be used to evaluate the possibility of RA in a subject, and therefore does not teach or suggest the invention of claim 7.

Reconsideration and withdrawal of the rejection is proper and such action is requested.

CONCLUSION

Early and favorable consideration of the application is earnestly solicited.

While no extension of time is believed to be required, Applicants request any extension of time necessary for this response to be considered timely filed. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Reference No. 61646 (70904), Customer No. 21874.

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Respectfully submitted,

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